Diagnosis of Tuberculous Uveitis: Clinical Application of an Interferon-gamma Release Assay

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Purpose: To determine the role of the QuantiFERON-TB Gold In-Tube (QFT) (Cellestis Inc., Carnegie, Australia) assay in the diagnosis of tuberculosis (TB) uveitis.

Design: Retrospective cohort study.

Participants: The study included 157 patients with suspected TB uveitis seen over an 18-month period (August 1, 2006, to February 31, 2007) at the Singapore National Eye Center (SNEC) uveitis clinic.

Methods: We identified all cases of suspected TB uveitis in the above-mentioned time period and reviewed all medical records of the cases. Clinical findings, type of treatment instituted, response to treatment, and results of investigations such as QFT, tuberculin skin test (TST), and chest x-rays were recorded. A novel method of using treatment response to determine the presumed diagnosis of TB was used to estimate the accuracy of QFT and TST.

Main Outcome Measures: The positive likelihood ratio (LR+), negative likelihood ratio (LR−), and area under the receiver operator characteristic curve (ROC) of the investigations were estimated.

Results: QFT is not superior to the TST in sensitivity as a screening test or first-line study in TB-related uveitis; however, QFT is more specific than the TST in identifying infections by *Mycobacterium tuberculosis.* Negative QFT tests should be interpreted with caution, because they do not exclude the diagnosis.

Conclusions: The new QFT is only slightly superior to the TST in the diagnosis of TB uveitis. Thus, there is an important role for interpreting the QFT together with the TST. This is the first and largest study of its kind to evaluate the use of QFT in the clinical diagnosis of TB uveitis.

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Tuberculosis (TB) is a resurgent disease in the developed world. The World Health Organization estimates that one third of the world's population is currently infected, with 9 million new cases occurring annually, leading to 3 million deaths per year.[1] However, it is estimated that only 10% of patients infected with *Mycobacterium tuberculosis* develop active disease.[1,2]

The clinical diagnosis of ocular TB is difficult. The manifestations in the eye are protean and can mimic other conditions.[2] As such, the ophthalmologist relies on clinical history, systemic examination, and screening investigations such as chest radiographs and the tuberculin skin test (TST).[2,3] A definite diagnosis of TB uveitis can be confirmed by performing acid-fast smears, mycobacterial cultures, or polymerase chain reaction-based assays on ocular fluid samples.[2] The current clinical gold standard for diagnosing a presumed TB uveitis requires a positive TST and supportive clinical ocular findings.[3]

New diagnostic tests for TB include interferon-γ release assays (IGRAs), such as the QuantiFERON-TB Gold In-Tube (QFT) (Cellestis Inc., Carnegie, Australia) and ELISpot^{PLUS} (T-SPOT.*TB*, Oxford Immunotec, Abingdon, U.K.).[4] The QFT is approved for use in the United States (Food and Drug Administration, 2007) and in many countries around the world.[4] The U.S. Centers for Disease Control recommends the IGRAs "to be used in all cases where the TST is to be used," whereas in the United Kingdom IGRAs are only indicated if the TST is positive.[4–6] The role of IGRAs in the diagnosis of TB uveitis is not well studied. We examined the role of the new QFT in the diagnosis of TB uveitis using a novel approach in a TB-endemic, cosmopolitan population.[1,7]

Materials and Methods

Study Design

This is a retrospective case series with suspected TB uveitis seen at the Singapore National Eye Center (SNEC) Uveitis clinic. This study was approved by the institution's ethics commitee. Patients were diagnosed with suspected TB uveitis with presenting clinical signs as suggested by Tabbara.[2] Our clinic adopts a standard questionnaire for all new cases, and those with uveitis have chest radiographs and the TST performed. QFT was performed in all suspected TB uveitis cases.

All new cases between August 1, 2006, and February 31, 2007, were enrolled. QFT and TST results were identified from the SNEC uveitis database. Patients' records were retrieved and data were recorded, which include demographics, QFT and TST results, erythrocyte sedimentation rate, hemoglobin levels, and steroid treatment with outcome monitored for a period of 12 months or

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completion of anti-TB therapy (ATT) for 6 months, whichever shorter. All patients were managed by 1 investigator (SPC). Data collection and analysis were performed by 1 investigator who was masked to the patients (MA).

All patients with suspected TB uveitis were referred to infectious disease physicians in the Singapore General Hospital, who made independent diagnoses of TB using standard recommended guidelines,[6] based on clinical findings, screening, or confirmatory investigations. The decision to treat the patients was then independently made by the physician, using recommended[6] ATT (isoniazid 75 mg once daily [OD], rifampicin 150 mg OD, pyrazinamide 400 mg OD, ethambutol 275 mg OD) for at least 6 months. Patients who defaulted the 6-month post-completion of ATT follow-up, with no record of treatment outcome, were excluded from the study. Systemic steroids were commenced if the patient did not respond clinically to ATT. Oral prednisolone was used as the systemic steroid, usually with a starting dose of 1 mg/kg body weight, tapering slowly over the clinical course, or periocular steroid injections (triamcinolone acetonide, 10 mg/ml). The decision and dose for steroid therapy were dependent on the response, severity, or laterality.

The diagnosis of presumed TB uveitis is made in patients with supportive clinical findings and a positive clinical response to ATT in 4 to 6 weeks, in the absence of other confirmatory investigations.[3] In our study, the definition of a positive treatment response is a clinical resolution of ocular inflammation with ATT with or without steroids, with no clinical recurrence 6 months after completion of ATT. We then studied the results of QFT and TST in our subjects and whether the eventual diagnosis of a presumed TB uveitis was accurately identified. Figure 1 illustrates the division of subjects into 4 groups according to their test results and subdivision of the groups according to the eventual diagnoses. True positives were treated subjects without recurrence, and true negatives were untreated subjects without recurrence. False positives were treated subjects with recurrence, and false negatives were untreated subjects without recurrence.

Definitions of QFT results followed Centers for Disease Control recommendations.[4] Subjects with indeterminate QFT results were excluded from the study. TST was performed as part of routine screening at the SNEC uveitis clinic by using the standard Mantoux method:[8] intradermal injection of 0.1 ml (5 tuberculin units) purified protein derivative (RT23 SSI–2T.U. /0.1 ml Statens

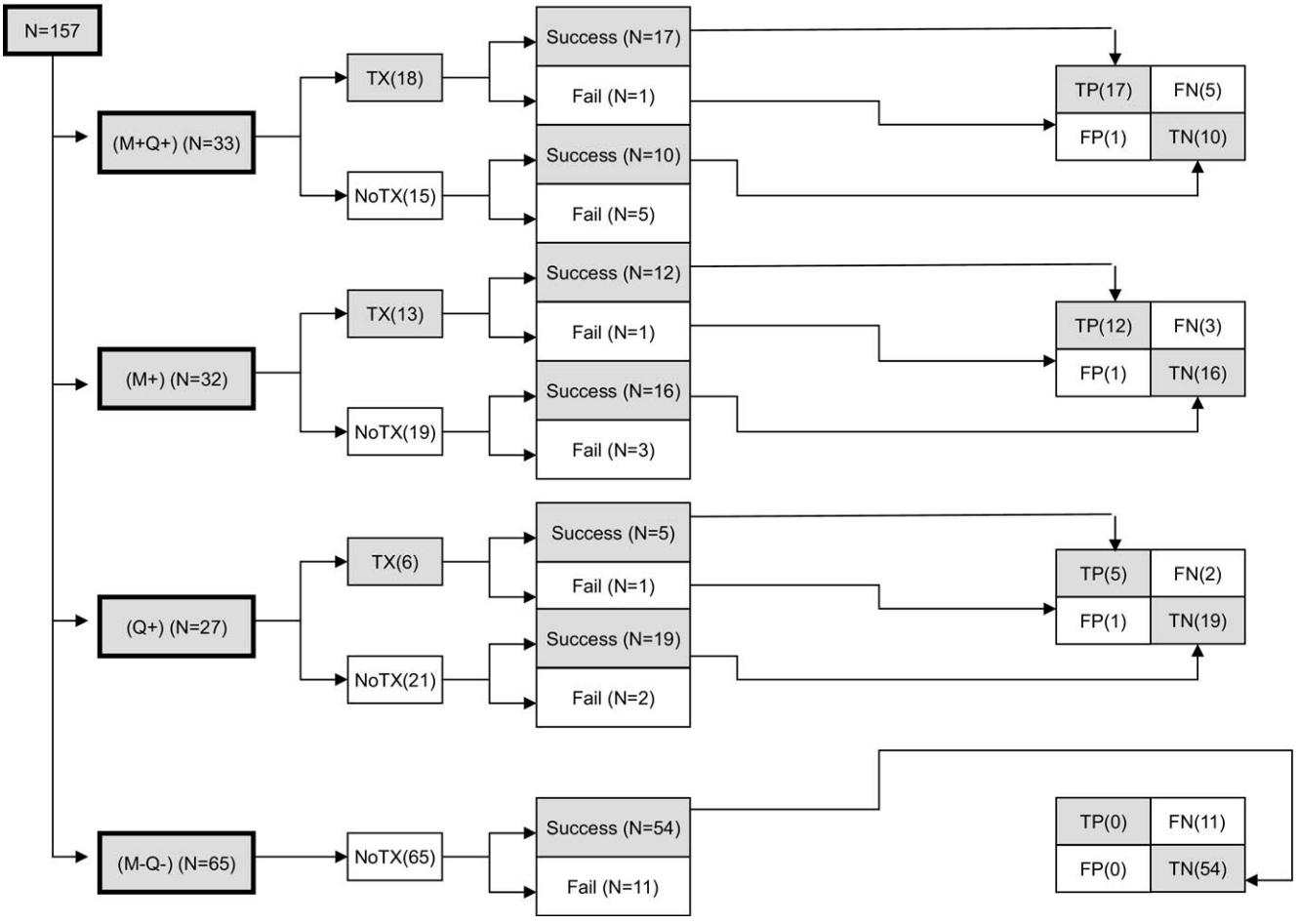

Figure 1. The division of subjects into 4 main groups according to the results of each test. Each group is then subdivided according to the eventual diagnoses. N = number of patients in study cohort; M = tuberculin/Mantoux skin test (TST); Q = QuantiFERON Gold In-Tube test (QFT; Cellestis Inc., Carnegie, Australia); TX = treatment as defined as recommended anti-TB treatment (isoniazid 75 mg OD, rifampicin 150 mg OD, pyrazinamide 400 mg OD, ethambutol 275 mg OD) for at least 6 months; success = a successful treatment response is defined as a clinical resolution of ocular inflammation with anti-TB treatment with or without steroids, with no recurrence 6 months after completing anti-TB treatment; failure = a failed treatment response is defined as no clinical resolution of ocular inflammation with anti-TB treatment with or without steroids or recurrence 6 months after completing anti-TB treatment; TP = true positive; TN = true negative; FP = false positive; FN = false negative.